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(54) Title: LUTEIN/ZEAXANTHIN FOR GLARE PROTECTION

(57) Abstract: The invention relates to the improvement of visual performance, particularly of visual performance in the darkness, by administration of a colorant that is capable of being incorporated into eye tissue and/or causing yellowing of eye tissue, especially carotenoids, such as lutein and zeaxanthin.

Lutein/Zeaxanthin for glare protection

The present invention relates to the improvement of visual performance. More particularly, the present invention relates to the improvement of visual performance in the darkness, e.g., when steering a vehicle or aircraft under low or dim light conditions such as at night or dawn, or when steering a vehicle in tunnels.

In accordance with the present invention it has been found that administration of a colorant that is capable of being incorporated into eye tissue and/or causing yellowing of eye tissue results in an improvement of visual performance. A common feature of such colorants is that they when deposited in the eye tissue, particularly the retina, provide a yellow filter that absorbs blue light. Blue light is supposed to be potentially damaging to the retina. Examples of colorants that can be used in accordance with the present invention are carotenoids, such as lutein, zeaxanthin, mesozeaxanthin, astaxanthin, or esters thereof, or canthaxanthin, or mixtures of the foregoing, as well as compounds having vitamin A activity, or precursors thereof. Administration of lutein and zeaxanthin has been found to lower the risk for developing age-related macular disease (AMD). However, these compounds are useful to improve visual performance also in the absence of AMD. Accordingly, in one aspect the present invention relates to the use of colorant that is capable of being incorporated into eye tissue and/or causing yellowing of eye tissue, particularly a carotenoid such as a compound selected from lutein, zeaxanthin, mesozeaxanthin, astaxanthin, or esters thereof, or canthaxanthin, or mixtures of the foregoing, and/or a compound having vitamin A activity, or precursor thereof, in the manufacture of a composition for improving visual performance in the darkness. In another aspect, the present invention relates to a method of improving visual performance in the darkness, by administration of an effective amount of one or more of the aforesaid colorants.

In a further embodiment, the present invention relates to the use of a the aforementioned colorants in combination with an anti-oxidant selected from vitamin E, vitamin C, a zinc

or anorganic selenium salt such as selenophosphates or sodium selenite or sodium selenateor seleno aminoacids such as L-selenomethionine, or selenized yeast such as brewer's yeast or baker's yeast (Saccharomyces cerevisiae) containing or enriched in selenium ,and bilberry extract containing approx 20 to 30 anthocyanosides, or mixtures thereof in the manufacture of a composition for improving visual performance.

Esters of lutein, zeaxanthin, mesozeaxanthin or astaxanthin are preferably esters of saturated alkanoic acids such as acetic, propionic, palmitic, stearic and succinic acid, mono-unsaturated fatty acids such as oleic acid, and poly-unsaturated fatty acids such as linolic, linoleic, docosahexaenoic and arachidonic acid.

Examples of compounds having vitamin A- activity or precursors thereof are retinol and esters thereof, such as retinyl palmitate; α- and β-carotene, β-cryptoxanthin, and lycopene. Examples of zinc salts are zinc salts of mineral acids such as zinc sulfate, or of organic acids such as zinc orotate. Examples of organic selenium salts are selenophosphates or sodium selenite or sodium selenate.

The term "vitamin E" refers to natural or racemic α-tocopherol as well as esters thereof such as the acetate. The term "vitamin C" comprises ascorbic acid and esters and salts thereof such as ascorbyl palmitate and sodium ascorbyl phosphate.

The term "visual performance" as used herein refers to visual functions such as acuity, contrast sensitivity, dark adaptation, glare recovery, photostress recovery, retinal sensitivity, blue cone sensitivity, color vision and visual field. Of particular interest is recovery from and the reduction of the physiological effects of glare, especially glare caused by blue light, e.g., when driving in the darkness, i.e. at night or dawn, or in tunnels. Another visual function that may be improved in accordance with the present invention is accuracy in target shooting.

The term "eye tissue" comprises retina, lens, vitreous, retinal pigment epithelium, iris and ciliary body.

The term "composition as used herein denotes any composition that is suitable for administration to the human body, such as pharmaceutical preparations, food or beverage.

A pharmaceutical preparation in accordance with the present invention for improvement of visual performance may be in any form that is conventional for oral administration, e.g. in solid form such as tablets including effervescent tablets, or soft or hard shell capsules, or in liquid form, such as solutions or suspensions, preferably oily suspension. Besides the

active ingredients the pharmaceutical preparation may contain conventional pharmaceutical carrier material, additives and adjuvants, which include water, gelatin, vegetable gums, sugars, vegetable oils,polyalkylene glycols, flavoring agents, preservatives, stabilizers, emulsifying agents, buffers and the like. The medicaments may be in the form of controlled (delayed) release formulations. For the purpose of the invention the colorants as well as optional ingredients as defined earlier hereinabove may be incorporated in food or beverages, such as bakery items, e.g., cake and cookies, lemonades and fruit juices.

In a preferred aspect, the invention relates to the use of colorants as defined earlier hereinabove in the manufacture of a medicament, a food or beverage for reducing glare or promoting recovery from glare in driving at night. Preferably, a combination of lutein and zeaxanthin is used. In such combination these compounds are preferably used in a ratio of 0.1-1.0 : 1.0- 0.1 parts by weight.

In solid pharmaceutical preparations, the compounds selected from lutein, zeaxanthin, mesozeaxanthin, astaxanthin, β-cryptoxanthin or esters thereof, or canthaxanthin are suitably present in an amount from about 0.1 mg to about 500 mg, preferably from about 1 mg to about 100 mg per dosage unit. In liquid formulations, the aforesaid ingredients are suitably present in an amount of from about 0.1 to about 5 percent by weight based upon the total weight of the composition. If vitamin E is present, its amount is suitably from about 10 to about 1000 mg per dosage unit in solid formulations and from about 0.1 to about 500 mg in liquid formulations. In liquid formulations vitamin E may serve as a carrier for other lipophilic components of the formulations in accordance with the invention and may comprise 99,9 – 50% percent by weight based upon the total weight of the composition. If vitamin C is present, its amount is suitably from about 10 to about 1000 mg per dosage unit. Compounds having vitamin A activity or precursors thereof may be present in amounts providing a vitamin A activity of from about 100 to about 10000 International Units per dosage unit. Zinc may be present in an amount of 1 to 100 mg (based on elementary zinc) per dosage unit. Selenium may be present in an amount of 10 to 200 microgram mg (based on elementary selenium) per dosage unit. Bilberry extract may be used in amounts of 50 to 150 mg (usually containing 20 to 30% anthocyanosides) per dosage unit.

Preferred solid pharmaceutical preparations comprise, per dosage unit, about 6 mg to about 12 mg of lutein, zeaxanthin, mesozeaxanthin, astaxanthin β-cryptoxanthin or esters thereof, or canthaxanthin, or mixtures of the foregoing; about 200 mg of vitamin E; and 1

mg to about 10 mg of zinc, and, optionally, about 1000 International Units of vitamin A and further optionally, about 1 mg to about 10 mg of β-carotene. Thus, in a further aspect, the present invention also relates to such preferred solid pharmaceutical preparations.

A suitable daily dosage of the ingredients, lutein, zeaxanthin, mesozeaxanthin, astaxanthin β-cryptoxanthin or esters thereof, or canthaxanthin in a pharmaceutical preparation prepared in accordance with the present invention or contained in any food or beverage is, e.g.,within the range of from 0.001 mg per kg body weight to about 20 mg per kg body weight. More preferred is a daily dosage of about 0.01 to about 10 mg per kg body weight, and especially preferred is about 0.1 to 1.0 mg per kg body weight per day, based upon the total weight of these components in their unesterified form.

The invention is illustrated further by the Examples given below:

Example 1

A soft gelatin capsule may be prepared comprising the following ingredients:

Ingredient	Amount per Capsule
Lutein	10 mg
Lecithin	50 mg
Soy bean oil	200 mg

Example 2

A soft gelatin capsule may be prepared comprising the following ingredients:

Ingredient	Amount per Capsule
Lutein	10 mg
Zeaxanthin	10 mg
Lecithin	50 mg
Soy bean oil	200 mg

Example 3

A soft gelatin capsule may be prepared comprising the following ingredients:

Ingredient	Amount per Capsule
Lutein	6 mg
Zeaxanthin	6 mg
Vitamin E (α-d,l-tocopherol)	200 mg
Vitamin C	500 mg
Lecithin	50 mg
Soy bean oil	200 mg

Example 4

A soft gelatin capsule may be prepared comprising the following ingredients:

Ingredient	Amount per Capsule
Lutein	12 mg
Vitamin E (α-d,l-tocopherol)	200 mg
Vitamin C	500 mg
Lecithin	50 mg
Soy bean oil	200 mg

Example 5

A soft gelatin capsule may be prepared comprising the following ingredients:

Ingredient	Amount per Capsule
Zeaxanthin	12 mg
Vitamin E (α-d,l-tocopherol)	200 mg
Vitamin C	500 mg
Lecithin	50 mg
Soy bean oil	200 mg

Example 6

A soft gelatin capsule may be prepared comprising the following ingredients:

Ingredient	Amount per Capsule
Lutein	6 mg
Zeaxanthin	6 mg
β-Carotene	6 mg
Vitamin E (α-d,l-tocopherol)	200 mg
Vitamin C	500 mg
Zinc (as orotate)	7.5 mg
Lecithin	50 mg
Soy bean oil	200 mg

Example 7

A soft gelatin capsule may be prepared comprising the following ingredients:

Ingredient	Amount per Capsule
Lutein	6 mg
Zeaxanthin	6 mg
Vitamin E (α-d,l-tocopherol)	200 mg
Vitamin C	500 mg
Vitamin A	1000 Int. Units
Zinc (as orotate)	7.5 mg
Lecithin	50 mg
Soy bean oil	200 mg

Example 8

A soft gelatin capsule may be prepared comprising the following ingredients:

Ingredient	Amount per Capsule
Lutein	6 mg
Zeaxanthin	6 mg
β-Carotene	6 mg
Vitamin E (α-d,l-tocopherol)	200 mg
Vitamin C	500 mg
Vitamin A	1000 Int. Units
Zinc (as orotate)	7.5 mg
Lecithin	50 mg
Soy bean oil	200 mg

What is claimed is:

1. The use of a colorant that is capable of being incorporated into eye tissue and/or causing yellowing of eye tissue, in the manufacture of a composition for the improvement of visual performance in the darkness.

2. The use according to claim 1 wherein the improvement is in reducing glare or promoting recovery from glare, particularly when steering a vehicle or aircraft under low or dim light conditions.

3. The use according to claim 1 or 2 wherein the colorant is a carotenoid.

4. The use according to any one of claims 1-3 wherein the colorant is selected from lutein, zeaxanthin, mesozeaxanthin, astaxanthin, or esters thereof, or canthaxanthin, or from compounds having vitamin A activity or precursors thereof, or mixtures of the foregoing.

5. The use according to claim 4 wherein the colorant selected from compounds having vitamin A activity or precursors thereof is retinol or esters thereof, such as retinyl palmitate; α- and β-carotene, β-cryptoxanthin, or lycopene, or mixtures of the foregoing.

6. The use according to any one of claims 1-5 which comprises additionally an anti-oxidant selected from vitamin E, vitamin C, a zinc or selenium salt or a selenium aminoacid, selenized yeast and bilberry extract, or mixtures thereof.

7. The use according to any one of claims 1-6, wherein the compound is lutein or zeaxanthin, or ester of lutein or zeaxanthin, or any combination thereof.

8. The use according to claim 7 of a combination of lutein and zeaxanthin.

9. The use according to any one of claims 1-8 wherein the composition is a pharmaceutical composition.

10. The use according to claim 9 wherein the pharmaceutical composition is for oral application and contains per dosage unit an amount of about 0.1 mg to about 500 mg of lutein, zeaxanthin, mesozeaxanthin, astaxanthin, or esters thereof, or canthaxanthin, or mixtures of the foregoing.

11. The use according to claim 9 or 10 wherein the composition contains a compound having vitamin A activity or precursor thereof particularly retinol and esters thereof, such as retinyl palmitate; α- and β-carotene, β-cryptoxanthin, and lycopene or mixtures of the foregoing in an amount providing a vitamin A activity of about 100 to about 10000 International Units of vitamin A per dosage unit.

12. The use according to any one of claims 9-11 wherein in the composition additionally contains about 10 mg to about 1000 mg of vitamin E per dosage unit.

13. The use according to any one of claims 9-12 wherein the composition additionally contains about 1 mg to about 100 mg of zinc per dosage unit.

14. The use according to any one of claims 1-8 wherein the composition is a food or beverage.

15. A solid pharmaceutical composition comprising, per dosage unit, about 6 mg to about 12 mg each of lutein and zeaxanthin; about 200 mg of vitamin E; and 1 mg to about 10 mg of zinc.

16. A composition according to claim 15 comprising additionally about 1000 International Units of vitamin A per dosage unit

17. A composition according to claim 15 or 16 comprising additionally about 1 mg to about 10 mg of β-carotene per dosage unit.

18. A method of improving visual performance in the darkness which comprises administering to a person in need of such treatment an effective amount of a colorant that is capable of being incorporated into eye tissue and/or causing yellowing of eye tissue

19. The method according to claim 18 wherein the improvement is in reducing glare or promoting recovery from glare, particularly when steering a vehicle or aircraft under low or dim light conditions.

20. The method according to claim 18 or 19 wherein the colorant is a carotenoid.

21. The method according to any one of claims 18-20 wherein the colorant is selected from lutein, zeaxanthin, mesozeaxanthin, astaxanthin, or esters thereof, or canthaxanthin, or from compounds having vitamin A activity or precursors thereof, or mixtures of the foregoing.

22. The method according to any one of claims 18-20 wherein the colorant selected from compounds having vitamin A activity or precursors thereof is retinol or esters thereof, such as retinyl palmitate; α- and β-carotene, β-cryptoxanthin, or lycopene, or mixtures of the foregoing.

23. The method according to any one of claims 18-22 which comprises additionally administering an anti-oxidant selected from vitamin E, vitamin C, a zinc or selenium salt, or a selenium aminoacid, selenized yeast and bilberry extract, or mixtures thereof.

24. The method according to any one of claims 18-23, wherein the colorant is lutein or zeaxanthin, or ester of lutein or zeaxanthin, or any combination thereof.

25. The method according to claim 24 wherein the colorant is a combination of lutein and zeaxanthin.

26. A method according to any one of claims 18-25, wherein the daily dosage of colorant is within the range of from 0.001 mg per kg body weight to about 20 mg per kg body weight, preferably from about 0.01 to about 10 mg per kg body weight, and most preferably from about 0.1 to 1.0 mg per kg body weight per day, based upon the total weight of the colorant in its unesterified form.

27. The invention substantially as described herein especially with reference to the Examples.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/00656

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/07 A61P27/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, EPO-Internal, PAJ, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HEINERMANN P.H.: "YELLOW INTROCULAR FILTERS IN FISHES" EXPERIMENTAL BIOLOGY, vol. 43, no. 2, 1984, pages 127-147, XP002242363 GERMANY page 127, paragraph 2 page 128, paragraph 1 page 140, line 5 - line 9 page 141, paragraph 3 page 142, paragraph 2 --- -/--	1-13, 18-26

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 May 2003	11/06/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Economou, D

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/00656

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RICHER S.: "armd-pilot (case series) enviromental intervention data" JOURNAL OF THE AMERICAN OPTOMETRIC ASSOCIATION, vol. 70, no. 1, January 1999 (1999-01), pages 24-36, XP009011053 usa the whole document	1-26
X	HAMMOND, B.R. ET AL.: "DENSITY OF THE HUMAN CRYSTALLINE LENS IS RELATED TO THE MACULAR PIGMENT CAROTENOIDS, LUTEIN AND ZEAXANTHIN" OPTOMETRY AND VISION SCIENCE, vol. 74, no. 7, 1997, pages 499-504, XP009011411 USA abstract page 499, left-hand column, line 10 - line 13 page 500, left-hand column, paragraph 3 -right-hand column, paragraph 1 page 502, right-hand column, paragraph 3 -page 503, last paragraph	1-26
X	OLMEDILLA, B. ET AL.: "LUTEIN IN PATIENTS WITH CATARACT AND ADE-RELATED MACULAR DEGENERATION: A LONG-TERM SUPPLEMENTATION STUDY" JOURNAL OF THE SCIENCE OF FOOD AND AGRICULTURE, vol. 81, no. 9, July 2001 (2001-07), pages 904-909, XP002242364 abstract page 904, left-hand column, line 1 -right-hand column, paragraph 2 page 905, left-hand column, paragraph 4 page 905, left-hand column, paragraph 5 -right-hand column, line 2 page 905, right-hand column, last paragraph -page 908, right-hand column, last paragraph	1-26
X	GB 2 301 775 A (THE HOWARD FOUNDATION) 18 December 1996 (1996-12-18) the whole document	1-26

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/00656

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-2
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-2

Present claims 1-2 relate to a products/methods defined by reference to a desirable characteristic or property, namely the ability of the claimed colorants to be incorporated into eye tissue and/or causing yellowing of eye tissue and to improve visual performance in the darkness and to reduce glare or to promote recovery from glare.
The claims cover all products/methods having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products/methods/apparatus. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product/methods by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the products and methods relating to carotenoids (claim 2) or the compounds mentioned in claims 4-5 in connection to their alleged activities.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/00656

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2301775 A	18-12-1996	AU 719671 B2	18-05-2000
		AU 5907896 A	30-12-1996
		CA 2224217 A1	19-12-1996
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